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Cost-Effectiveness of Magnetic Resonance Angiography Versus Intra-arterial Digital Subtraction Angiography to Follow-Up Patients With Coiled Intracranial Aneurysms

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Background and Purpose**—**To follow up patients with coiled intracranial aneurysms, magnetic resonance angiography (MRA) is a promising noninvasive alternative to current standard intra-arterial digital subtraction angiography (IA-DSA). MRA test results do not always concord with those of IA-DSA, and the impact of discrepancies on health benefits and costs is unknown. We evaluated the cost-effectiveness of follow-up with MRA vs IA-DSA to assess whether in this setting MRA may replace IA-DSA.

Methods**—**We studied aneurysm occlusion on MRA in addition to follow-up IA-DSA in 310 patients with 341 coiled intracranial aneurysms. The observed sensitivity (82%) and specificity (89%) of MRA for detection of reopening with IA-DSA as a reference were used as input for a Markov decision-analytic model. Other determinants were derived from the literature. We compared life expectancy, quality-adjusted life-years (QALY), costs, and expected number of events for the two strategies.

Results**—**Follow-up with MRA yielded similar life expectancy (MRA, 26.66 years; IA-DSA, 26.63 years; difference, 0.03 years; 95% CI, −0.17–0.23) and QALY (MRA, 10.96; IA-DSA, 10.95; difference, 0.01 QALY; 95% CI, −0.05–0.08) at lower costs (MRA, $7003; IA-DSA, $8241 per patient; difference, −$1238; 95% CI, −2617-−36). The expected number of events was comparable except for complications from IA-DSA.

Conclusion**—**MRA provided equivalent health benefits as IA-DSA and was cost-saving. MRA dominates and should replace routine IA-DSA to follow-up patients with coiled aneurysms. **(*Stroke*. 2010;41:1736-1742.)**

Key Words: cost-benefit analysis ■ digital subtraction angiography ■ intracranial aneurysm ■ magnetic resonance angiography

Follow-up after occlusion of intracranial aneurysms with coils is required because reopening and subsequent rupture may occur.[1–3] Intra-arterial digital subtraction angiography (IA-DSA) is the standard modality to detect reopening after coiling but is invasive and irradiating.[4] Furthermore, the procedure may cause patient discomfort and requires substantial capacity of the angiography suite and inpatient clinic. Magnetic resonance angiography (MRA) is an alternative technique that is noninvasive, nonirradiating, and can be performed in an outpatient setting.

To investigate whether MRA can replace IA-DSA for follow-up of coiled patients, complete diagnostic evaluation of MRA is required. This should include assessment of its test characteristics, effect on clinical outcome, and cost-effectiveness.[5]

Although test characteristics have been reported, we could not find studies on effects on clinical outcome and cost-effectiveness in this clinical setting. In a large prospective series of patients, we have recently compared MRA and IA-DSA to assess reopening of coiled aneurysms.[6] This enabled us to use the observed test characteristics of MRA with IA-DSA as a reference to assess the expected changes in health benefits and costs incurred using MRA or IA-DSA.

Materials and Methods

Using a cross-sectional design, we previously assessed the accuracy for detection of reopened aneurysms in MRA with IA-DSA as a reference in 310 coiled patients (mean age, 51±12; 71% women).[6] Unenhanced (time-of-flight) and contrast-enhanced MRA were performed in each patient in addition to routine IA-DSA. Two observers classified, independently from each other, the level of occlusion as

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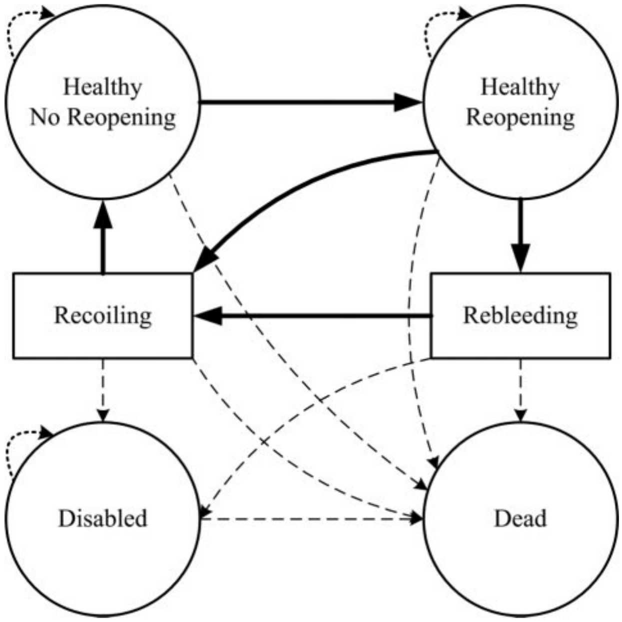

Figure 1. State transition model. Possible transitions between health states (circles) in our Markov model. Patients may develop reopening, remain in the same health state, or may move to the disability and death state because of complications of diagnostic testing, recoiling, rebleeding, or unrelated events.

adequate or reopening on IA-DSA and on MRA. They were blinded for the parallel imaging modality. Sensitivity of MRA for detection of reopened aneurysms was 82% (95% CI, 72%–89%) and specificity was 89% (95% CI, 85%–93%). Contrast-enhanced MRA did not provide additional information to unenhanced MRA. The mean residual lumen of undetected reopened aneurysms on MRA was 3 mm vs 6 mm for detected reopened aneurysms. Retreatment was performed when the residual lumen appeared large enough for additional coiling, which was the case in 44 of 76 patients (58%; 95% CI, 47%–68%) with reopened aneurysms on IA-DSA.

Evaluation of Health Benefits and Costs: A Markov Model

We developed a Markov decision-analytic model (TreeAge Software) to assess differences in health benefits and costs for follow-up with MRA vs follow-up with IA-DSA.[7] A Markov model is based on probabilities of transitions between health states that we predefined as "healthy with an occluded aneurysm," "healthy with a reopened aneurysm," "disabled" (severe disability requiring a nursing home), and "death" (Figure 1). To each health state we assigned a measure for utility that was ultimately used to estimate quality-adjusted life-years (QALY). Various events could cause transitions between health states, such as complications of the diagnostic procedure or treatment, recurrent subarachnoid hemorrhage, or unrelated events. The probabilities of occurrence of these events and their costs were the input parameters for the model. Then, a hypothetical cohort of patients was run through the model with 1-month time cycles. All started in "healthy with an occluded aneurysm" and could transit to other health states depending on occurring events. A lifetime horizon was used. This allowed us to simulate the individual life course of a large hypothetical cohort to assess the change in health benefits (QALY) and costs for a follow-up strategy with MRA vs IA-DSA.

Model Scenarios

In clinical practice, coiled patients are eligible for follow-up IA-DSA when they regain independence for daily activities after subarachnoid hemorrhage. In analogy to clinical practice, our model structure was as follows: fictive patients who were independent for daily activities entered the model at 6 months after coiling for the first follow-up procedure, which was either IA-DSA or MRA. In case of detected aneurysm reopening, patients could be recoiled. Recoiling was also considered for patients with a falsely assumed reopening on MRA. The coiling procedure that requires IA-DSA would be interrupted on detecting an aneurysm on IA-DSA that is actually sufficiently occluded. Conversely, undetected reopened aneurysms on MRA or untreated reopened aneurysms could cause recurrent subarachnoid hemorrhage. A second follow-up procedure was performed at 18 months after coiling. If the aneurysm was still occluded at 18 months of follow-up, then patients were discharged. Patients with untreated reopened aneurysms at 18 months after coiling were screened once more at 3.5 years after coiling. If the aneurysm was left untreated after the 3.5-year screening, then patients were discharged from follow-up. Complications of screening and recoiling procedures could cause disability and death (Figure 2).

Model Parameters

Age, gender, sensitivity and specificity of MRA, and probability of recoiling obtained from our clinical cohort were used as input parameters of the Markov model. Other input parameters on probabilities of health state transitions, utilities, and costs were derived from the literature after a systematic PubMed search. All parameters were discussed in a multidisciplinary setting (Table 1). For patients who died from unrelated causes, we used age- and gender-specific mortality rates provided by the national center of statistics in the Netherlands, adjusted for the standardized mortality ratios of patients after subarachnoid hemorrhage.[8]

The risk of reopening of coiled aneurysms decreases over time.[9–14] Based on the results of studies with different time intervals of follow-up, we developed a univariate regression function to predict long-term reopening risks after coiling (Supplemental Figure I, available online at http://stroke.ahajournals.org).

Direct medical costs were incorporated. Instantaneous costs were used for IA-DSA, MRA, recoiling, recurrent subarachnoid hemorrhage, and death. Long-term costs were used for disabled patients residing in a nursing home. All costs were updated to 2007 with Dutch inflation indices and converted to US dollars (1€=$1.38, June 2009; Table 1). Future costs and effects were discounted with 4% according to current Dutch guidelines.[15]

Model Assumptions

We assumed that reopened aneurysms do not occlude spontaneously because progressive occlusion is rare.[10,14] We furthermore assumed that the risk of rupture of reopened aneurysms is constant and similar for untreatable reopened aneurysms, undetected reopened aneurysms, or aneurysms that reopened after discharge from follow-up.

Model Simulation and Outcome Measures

In our baseline scenario, we evaluated the outcomes for 50-year-old patients with parameter values as in Table 1. Simulations were performed for 2500 hypothetical cohorts consisting of 5000 patients each. We compared life expectancy, health benefits in QALY, inherent costs, and the expected number of events for follow-up with IA-DSA and for follow-up with MRA.

We repeated the analysis for 35- and 65-year-old patient subgroups. We also performed cost-effectiveness analyses for the 3 age subgroups with a discount rate of 1.5% instead of 4% for costs and effects.[15] Because the aim of follow-up is to prevent recurrent subarachnoid hemorrhage, and because insufficient data on the rupture risk of reopened aneurysms were available, we repeated the analysis for different rupture rates.

Sensitivity Analyses

We explored uncertainty regarding the model input parameters with probabilistic sensitivity analysis using Monte Carlo simulation.[7,16] With Monte Carlo simulation, different samples are taken from parameter distributions for the hypothetical cohorts to assess uncertainty in cost-effectiveness estimates.

We performed additional univariate sensitivity analysis for all model parameters defined by distributions to evaluate the association

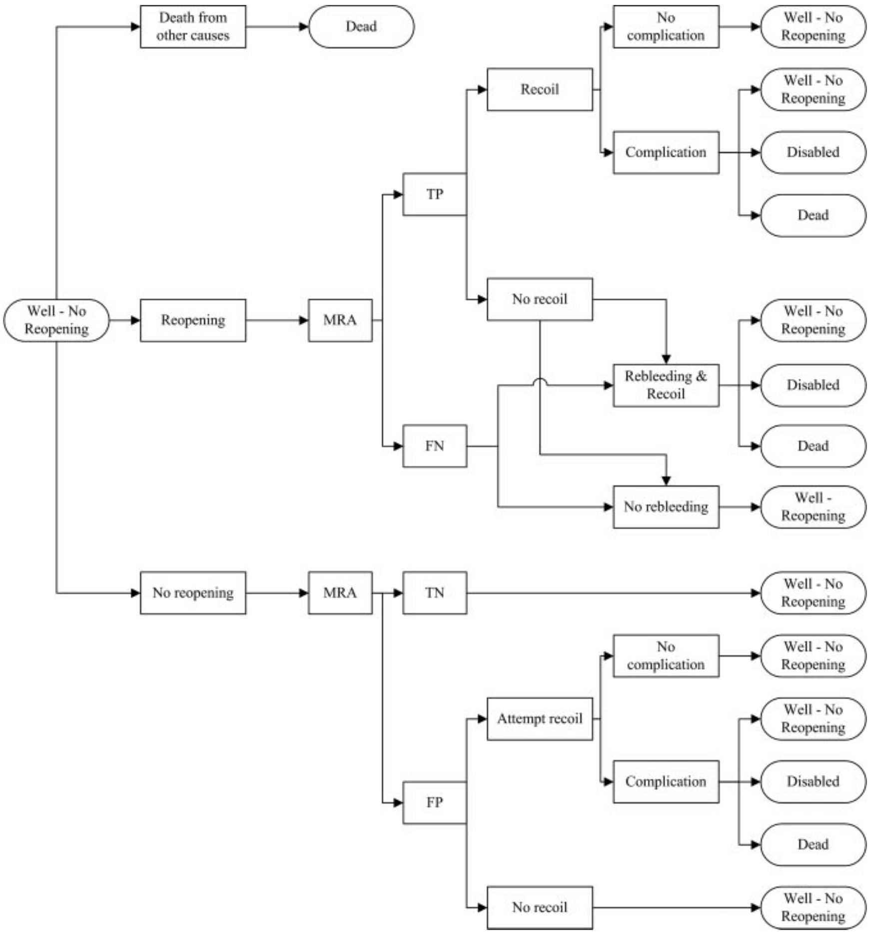

Figure 2. This simplified part of the decision tree used in the Markov model illustrates follow-up with MRA. TP, true-positive; FN, false-negative; TN, true-negative; FP, false-positive test result. The branch for IA-DSA is not displayed.

between the model parameters with associated uncertainty and changes in costs, effects in QALY, and cost-effectiveness.[16]

Results

For the baseline model, life expectancy and QALY were in the same range for follow-up with MRA and for follow-up with IA-DSA, whereas MRA significantly reduced costs (Tables 2 and 3, Figure 3).

MRA induced health gain while saving costs in 67% of our samples and induced health gain while increasing costs in 1%. Conversely, MRA reduced health benefits at lower costs in 31% of our samples and reduced health benefits at increased costs in 1% (Figure 3).

Life expectancy was 39.42 years (95% CI, 39.03–39.80) after IA-DSA vs 39.47 years (95% CI, 39.04–39.91) after MRA for 35-year old patients, 26.63 years (95% CI, 26.31–26.95) after IA-DSA vs 26.66 years (95% CI, 26.35–26.98) after MRA for 50-year-old patients, and 15.81 years (95% CI, 15.59–16.02) after IA-DSA vs 15.82 years (95% CI, 15.59–16.02) after MRA for 65-year-old patients.

The number of events during follow-up with IA-DSA and MRA was not different except for case fatality and morbidity caused by IA-DSA (Table 2). The incidence of recurrent subarachnoid hemorrhage was not significantly higher for MRA than for IA-DSA. The difference in the overall case fatality and morbidity between the diagnostic strategies was 9 out of 5000 patients in favor of follow-up by MRA.

Scenario analyses for different ages, discount rates, and rupture rates of reopened aneurysms yielded similar results as for the baseline model. MRA remained cost-saving with a similar change in QALY compared to IA-DSA (Table 3). For 50-year-old patients MRA gained slightly more QALY in 68%, for 35-year-old patients in 72%, and for 65-year-old patients in 64% of the sampled cohorts. The probability of health gain by MRA increases with decreasing age. The cost-saving provided by MRA was similar in all our scenarios and was apparently not largely influenced by patient age, the rupture risk, or the discount rate used in the model.

Sensitivity analysis demonstrated that the distribution of input parameters did not significantly influence costs or QALY. We did not find an association between values of single-model parameters and cost-effectiveness estimates.

Discussion

Follow-up after coiling of intracranial aneurysms by MRA results in similar health benefits but lower costs than follow-up by IA-DSA. The expected number of events was similar for both strategies, except for morbidity and case fatality caused by IA-DSA. Nevertheless, these complications did not have a major impact on cost-effectiveness because the total number of expected complications of IA-DSA remained small, particularly in comparison to patients with atherosclerosis.[4] The complication risk of MRA with contrast agent is extremely small.[17,18] We incorporated this small risk into the

Table 1. Model Input Parameters

Model Parameter	Value	95% CI/Range*	Distribution	Source
Probabilities				
Sensitivity MRA	0.82	0.72–0.89	Beta	CS
Specificity MRA	0.89	0.85–0.93	Beta	CS
P (case fatality of IA-DSA)	0.0006	0.0003–0.0010	Beta	4
P (morbidity of IA-DSA)	0.0010	0.0006–0.0015	Beta	4
P (case fatality of MRA)	0.0000000	. . .	. . .	17, 18
P (morbidity of MRA)	0.0000053	0.0000026–0.0000088	Beta	17, 18
P (case fatality recoiling)	0.0056	0.0018–0.0120	Beta	24–27
P (morbidity recoiling)	0.011	0.004–0.021	Beta	26, 27
P (case fatality rebleeding)				28
30–39 y	0.182	0.162–0.204	Beta	
40–49 y	0.225	0.211–0.240	Beta	
50–59 y	0.249	0.236–0.262	Beta	
60–69 y	0.317	0.310–0.324	Beta	
70–79 y	0.455	0.438–0.472	Beta	
>80 y	0.576	0.553–0.598	Beta	
P (morbidity rebleeding)	0.09	0.08–0.11	Beta	29, 30
P (case fatality disabled patients) per year	0.24	0.10–0.36	Uniform	28, 31
P (reopening) up to 6 mo after coiling†	0.119	0.097–0.144	Beta	10, 11, 13
P (reopening) 6–18 mo after coiling†	0.055	0.019–0.110	Beta	9, 11, 14
P (reopening) 18 mo–6 y after coiling†	0.036	0.010–0.078	Beta	12
P (recoiling reopened aneurysm)	0.58	0.47–0.68	Beta	CS
P (rupture risk reopening) per year	0.017	0.014–0.020	Uniform	10, 12, 22, 23, 32
Costs ($)				
Costs IA-DSA	$838	. . .	. . .	33
Costs MRA	$371	. . .	. . .	33
Costs of rebleeding including recoiling	$36 920	. . .	. . .	34, 35
Costs of elective recoiling	$12 646	. . .	. . .	33
Costs nursing home per year	$107 711	. . .	. . .	15
Costs of patient death	$3585	. . .	. . .	36
Utilities				
Well after subarachnoid hemorrhage	0.72	0.65–0.80	Triangular	37
Disabled	0.25	0.21–0.30	Triangular	37
Dead	0	. . .	. . .	
Discounting				
Cost discount per year	4%	. . .	. . .	. . .
Effect discount per year	4%	. . .	. . .	. . .

CS indicates data obtained from our clinical study; IA-DSA, intra-arterial digital subtraction angiography; MRA, magnetic resonance imaging.

*95% CI for beta distribution; range for uniform/triangular distribution.

†A mathematical function based on these results was used (provided online). All rates obtained were converted to probabilities per month.

model, even though in our clinical study and other studies contrast-enhanced MRA did not provide significant additional information for unenhanced MRA.[19,20] So, the administration of contrast agent is often unnecessary, which decreases the morbidity risk of MRA even further. Moreover, those reopened aneurysms on IA-DSA that were not identified on MRA did not significantly increase the expected incidence of subarachnoid hemorrhage for patients followed-up with MRA. As a result of less than optimal quality of life after subarachnoid hemorrhage, life expectancy considerably surpasses the number of QALY, regardless of the strategy.

MRA appeared to be cost-saving. Because the number of events does not largely differ between the two strategies, the difference in costs is likely to be caused by the lower costs of MRA compared to the IA-DSA procedure. When cost reduc-

Table 2. Costs and Effects for Follow-Up With IA-DSA vs MRA

	IA-DSA	MRA	Difference	95% CI
Life expectancy per patient, y	26.63	26.66	0.03	−0.17–0.23
QALY per patient	10.95	10.96	0.01	−0.05–0.08
Total case fatality strategy, n	125	120	−5	−24–13
Total morbidity strategy, n	38	34	−4	−16–11
Case fatality recoiling, n	5	5	0	−3–2
Morbidity recoiling, n	9	9	0	−4–3
Case fatality test, n	7	0	−7	−14–−2*
Morbidity test, n	11	0	−11	−20–−4*
Reopened aneurysms, n	1359	1360	1	−28–31
Recoiling procedures, n	728	718	−10	−29–7
Rebleedings, n	191	196	5	−12–22
Costs per patient	$8241	$7003	$−1238	−2617–−36*

The cost-effectiveness estimates based on simulations of 2500 cohorts of 5000 patients each.

IA-DSA, intra-arterial digital subtraction angiography; MRA, magnetic resonance imaging; QALY, quality-adjusted life-year.

*Statistically significant.

tion is not taken into consideration, there is still a substantial chance that MRA is the preferred strategy with a small gain in QALY, especially for younger patients.

We could not find other studies on cost-effectiveness of MRA vs IA-DSA after coiling. Using a Markov model, we integrated the best available evidence for computation of the expected long-term outcomes. A diagnostic, randomized, clinical trial, although theoretically more accurate, would be infeasible because a large number of participants and long follow-up is required to ascertain the incidence of rupture of undetected or untreated reopened aneurysms.[5]

We intended to construct a detailed Markov model that appropriately reflects clinical practice, although we faced some limitations. First, IA-DSA is not a perfect reference standard for follow-up of coiled aneurysms. For example, the 2-dimensional images restrict visualization of residual flow in case of superimposition of coils or surrounding arteries.[21] Consequently, discrepant results on MRA had to be labeled as "false-positive" or "false-negative," whereas MRA may provide the more realistic visualization. Thus, the model represented the least favorable scenario for MRA and therefore may underestimate its diagnostic performance. MRA still appeared dominant, thus strengthening the conclusion that MRA may replace IA-DSA.

Second, input parameters originated from our clinical study and from the literature. Because coiling has been available since 1992, only limited data on reopening and subsequent rupture rates more than 5 to 10 years after coiling are available.[1,2,10,22,23] Reopening rates could only be estimated from a few studies with a systematic long-term follow-up at fixed time intervals.[3,9–14]

Third, for the model, we assumed a similar rupture rate for aneurysms that reopened after follow-up for untreatable and for undetected reopened aneurysms, whereas the actual rupture risks may differ in each situation. Undetected reopened aneurysms in our clinical study were smaller and therefore probably had a lower rupture rate than larger reopened aneurysms that are left untreated. By assuming a similar rupture rate, we overestimated the health loss from undetected aneurysms when using MRA and therefore underestimated the health benefits provided by MRA. Repeated analyses for different rupture rates resulted in marginal and similar changes in QALY and costs. So, the uncertainty around the exact rupture rate did not influence the cost-effectiveness of MRA compared to IA-DSA. We furthermore assumed that reopened aneurysms never occlude spontaneously. In case of spontaneous occlusion, the potential hazard of a nonidentified reopened aneurysm on MRA would be smaller. So, again, we applied the least favorable scenario for MRA to avoid positive bias.

Table 3. Scenario Analyses

			Costs, $		QALY					
Age, y	DR, %	Rupture Risk*	IA-DSA	MRA	IA-DSA	MRA	ΔCosts	95% CI	ΔQALY	95% CI
35	4	0.017	8240	7001	13.40	13.42	−1238	(−2663–−75)	0.02	(−0.04–0.08)
50	4	0.017	8241	7003	10.95	10.96	−1238	(−2617–−36)	0.01	(−0.05–0.08)
65	4	0.017	8290	7015	7.95	7.96	−1275	(−2523–−199)	0.01	(−0.04–0.06)
35	1.5	0.017	11 322	10 068	20.76	20.79	−1254	(−2899–290)	0.03	(−0.09–0.13)
50	1.5	0.017	10 438	9153	15.29	15.31	−1284	(−2979–72)	0.02	(−0.08–0.12)
65	1.5	0.017	9743	8403	9.90	9.91	−1340	(−2894–−50)	0.01	(−0.06–0.09)
50	4	0.034	9284	8056	10.90	10.91	−1227	(−2588–−6)	0.01	(−0.05–0.07)
50	4	0.014	7897	6653	10.96	10.98	−1244	(−2295–−108)	0.02	(−0.05–0.09)
50	4	0.009	7546	6291	10.98	10.99	−1255	(−2492–−61)	0.01	(−0.05–0.07)
50	4	0.005	7135	5871	11.00	11.01	−1264	(−2677–−122)	0.01	(−0.05–0.08)

Each analysis comprised 1000 simulations for 5000 patients.

DR, discount rate; IA-DSA, intra-arterial digital subtraction angiography; MRA, magnetic resonance imaging; QALY, quality-adjusted life-year.

*Rupture risk of reopened aneurysm per year.

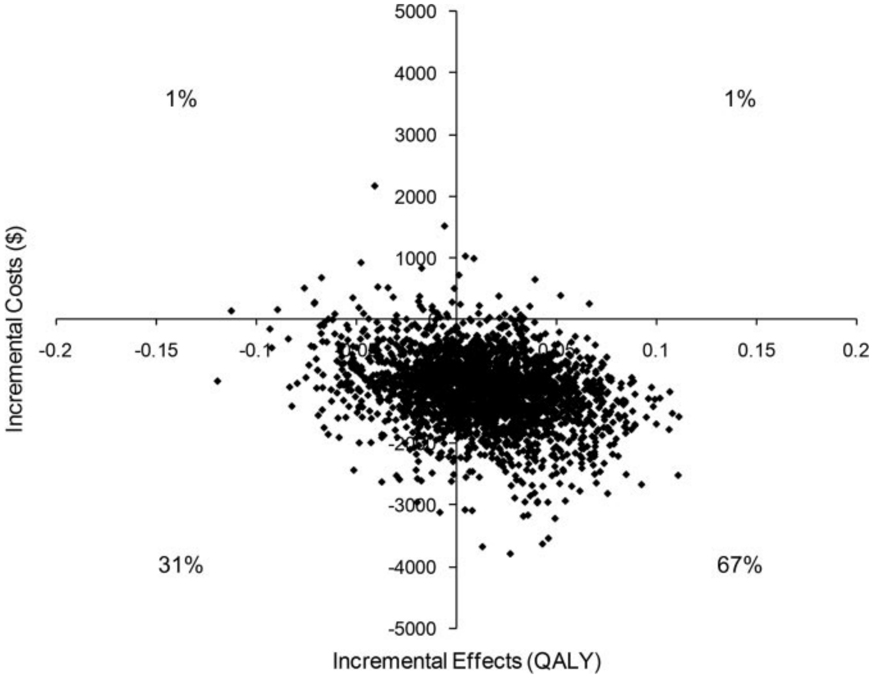

Figure 3. This cost-effectiveness graph shows the increment in QALY vs the increment in costs induced by MRA for 2500 simulations. Each dot represents one simulation for 5000 patients for which input values were sampled from the parameter distributions given in Table 1. The percentages of samples per quadrant are indicated.

Fourth, we did not evaluate the influence of uncertainty in costs on the cost-effectiveness of MRA vs IA-DSA because insufficient evidence was available to define their distribution. Finally, because information on actual dependencies between model parameters could not be obtained, all parameters were, by necessity, assumed to be independent in our probabilistic sensitivity analysis. This assumption may not hold for all parameters, eg, for sensitivity and specificity. Nevertheless, because the sensitivity analyses showed overall robust outcomes, we feel that our general conclusion remains justified.

MRA is a safe technique that can be performed in an outpatient setting. Our results show that the consequences of misdiagnosis by MRA outweigh the complications caused by IA-DSA and that MRA reduces costs. We therefore recommend using MRA instead of IA-DSA to follow-up coiled patients. The exact timing of reopening and subsequent rupture after coiling is unclear. Additional studies on timing of follow-up MRA are warranted to assess the short-term and long-term evolution of coiled aneurysms.

Conclusion

Cost-effectiveness analysis by Markov modeling shows that potential consequences of misdiagnosis by MRA will be offset by the direct risk of complications associated with IA-DSA, and MRA will reduce costs considerably. Patients therefore should be followed-up by MRA instead of IA-DSA to detect reopening after coiling of intracranial aneurysms.

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Disclosures

None.

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